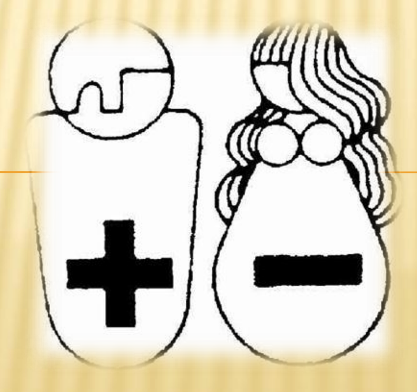
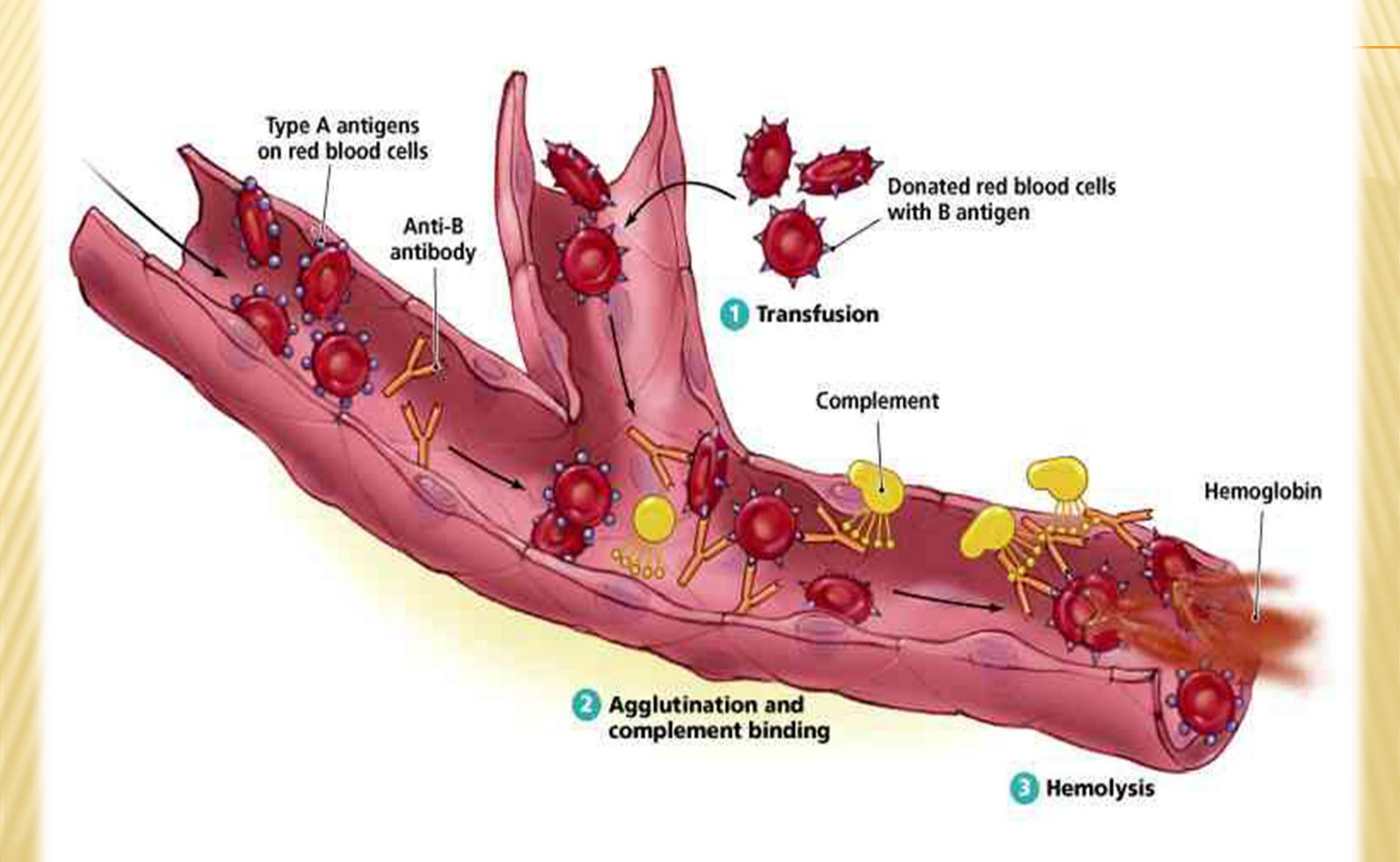
HEMOLYTIC DISEASE OF NEWBORN AND FETUS

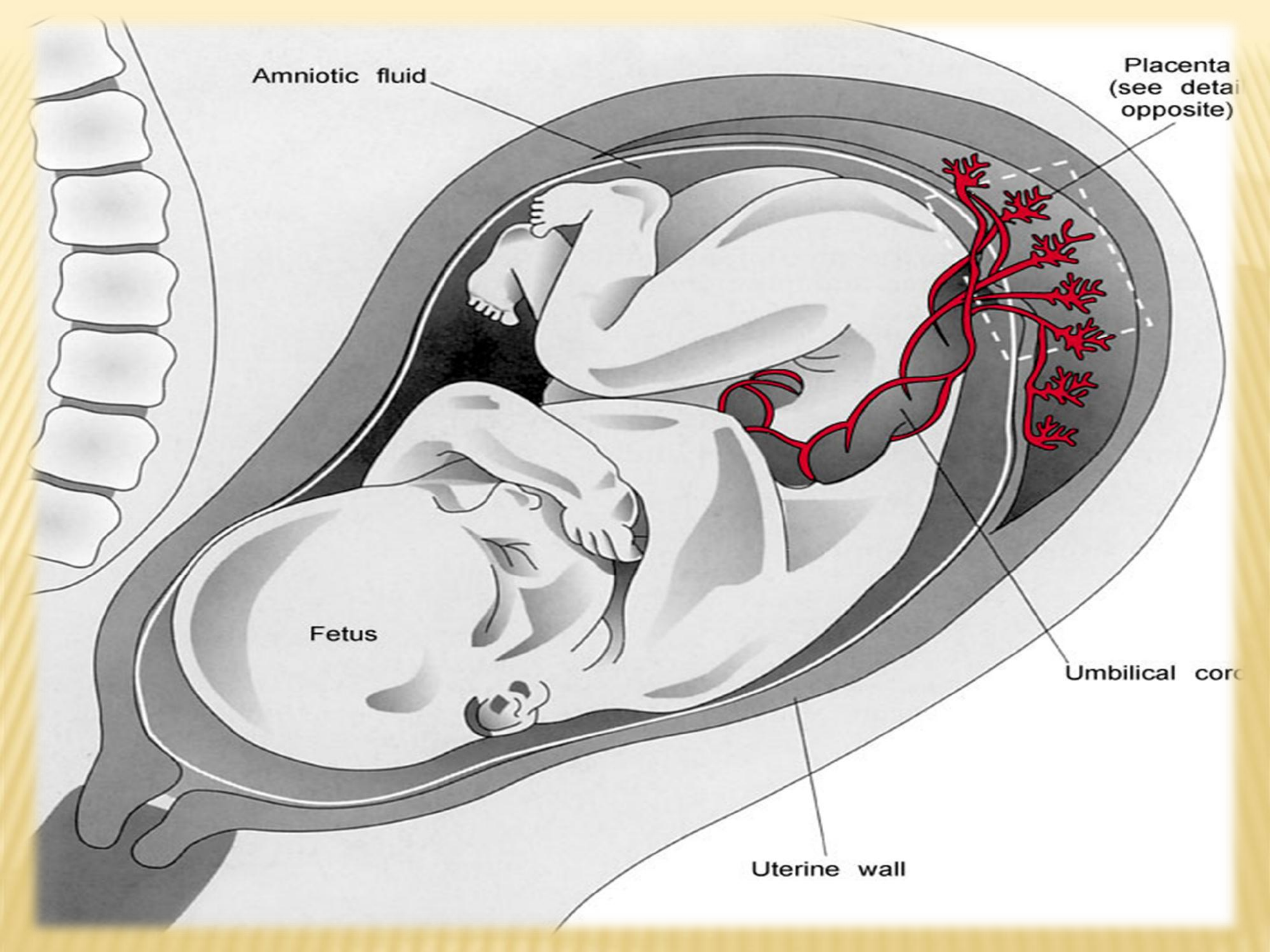
HDN



WHAT IS HDN?

- Destruction of the RBCs of the fetus and newborn by antibodies produced by the mother
- Only IgG antibodies are involved because it can cross the placenta (not IgA or IgM)


Type A antigens
on red blood cells
Anti-B
antibody
Donated red blood cells
with B antigen
1 Transfusion
Complement
Hemoglobin
2 Agglutination and
complement binding
3 Hemolysis


Amniotic fluid
Placenta
(see detai
opposite)
Fetus
Umbilical cor
Uterine wall

PATHOPHYSIOLOGY

- Although transfer of maternal antibodies is good, transfer of antibodies involved in HDN are directed against antigens on fetal RBCs inherited by the father
- Most often involves antigens of the Rh and ABO blood group system, but can result from any blood group system
- Remember: The fetus is POSITIVE for an antigen and the mother is NEGATIVE for the same antigen
- The mother is sensitized to the foreign antigen present on her child's RBCs usually through some seepage of fetal RBCs (fetomaternal hemorrhage) or a previous transfusion
- HDN occurs when these antibodies cross the placenta and react with the fetal RBCs.

ABO HDN

- ABO incompatibilities are the most common cause of HDN but are less severe.
- About 1 in 5 pregnancies are ABO-incompatible.
- 65% of HDN are due to ABO incompatibility.
  - **Usually, the mother is type O and the child has the A or B antigen…Why?**
- Group **O** individuals have a high titer of **IgG** anti-A,B in addition to having **IgM** anti-A and anti-B.
- ABO HDN can occur during the FIRST pregnancy prior sensitization is not necessary

ABO HDN

- ABO HDN is less severe than Rh HDN because there is less RBC destruction.
- Fetal RBCs are less developed at birth, so there is less destruction by maternal antibodies.
- When delivered, infants may present with mild anemia or normal hemoglobin levels.
- Most infants will have hyperbilirubinemia and jaundice within 12 to 48 hours after birth

DIAGNOSIS OF ABO HDN

- Infant presents with **jaundice** 12-48 hrs after birth.
- Testing done after birth on cord blood samples.

TREATMENT OF ABO HDN

- Only about 10% require therapy
- **Phototherapy** is sufficient, Phototherapy is exposure to artificial or sunlight to reduce jaundice.
- Rarely is exchange **transfusion** needed, Exchange transfusion involves removing newborn's RBCs and replacing them with normal fresh donor cells

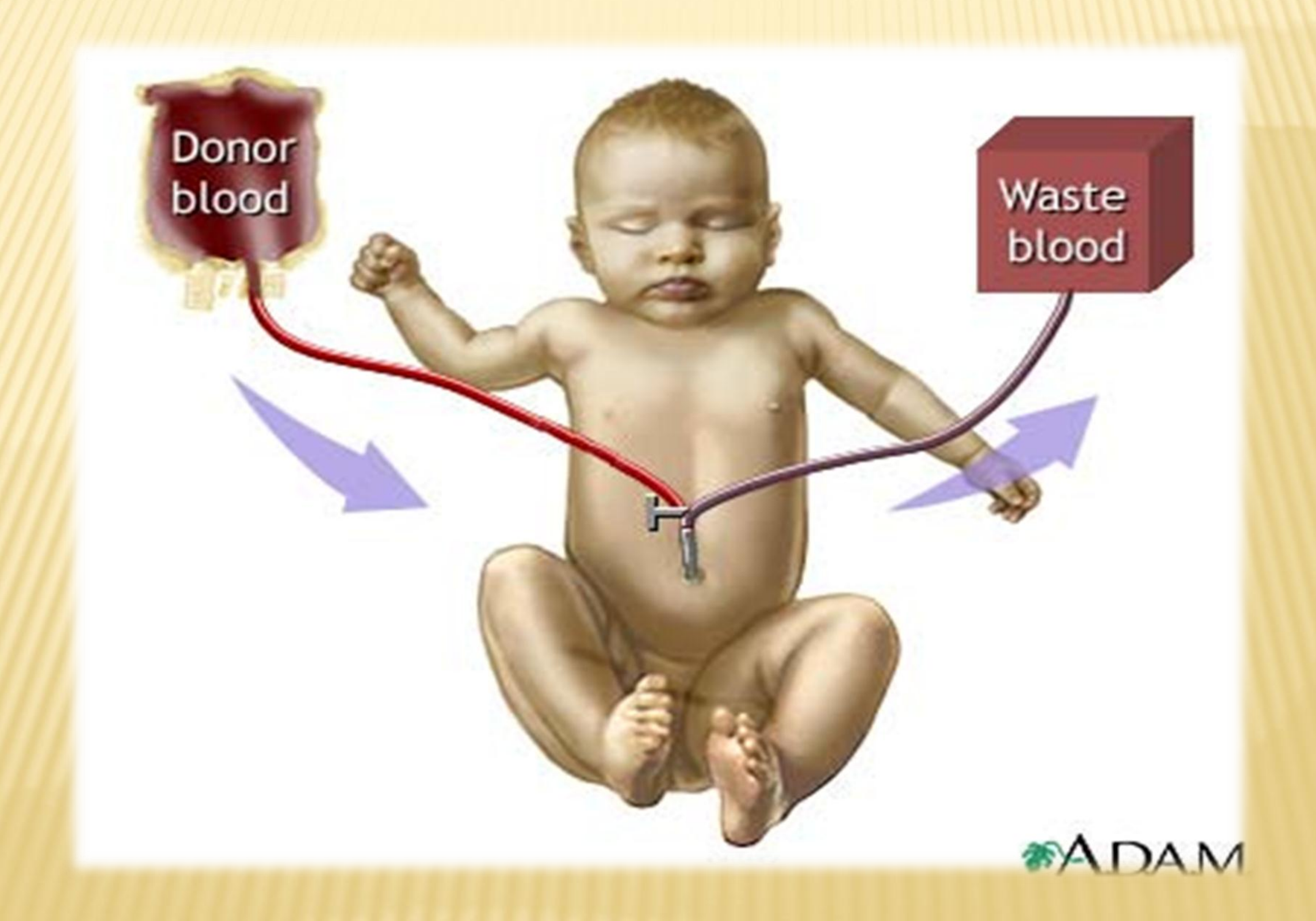
PHOTOTHERAPY





Fluorescent blue light in the 420-475 nm range

EXCHANGE TRANSFUSION

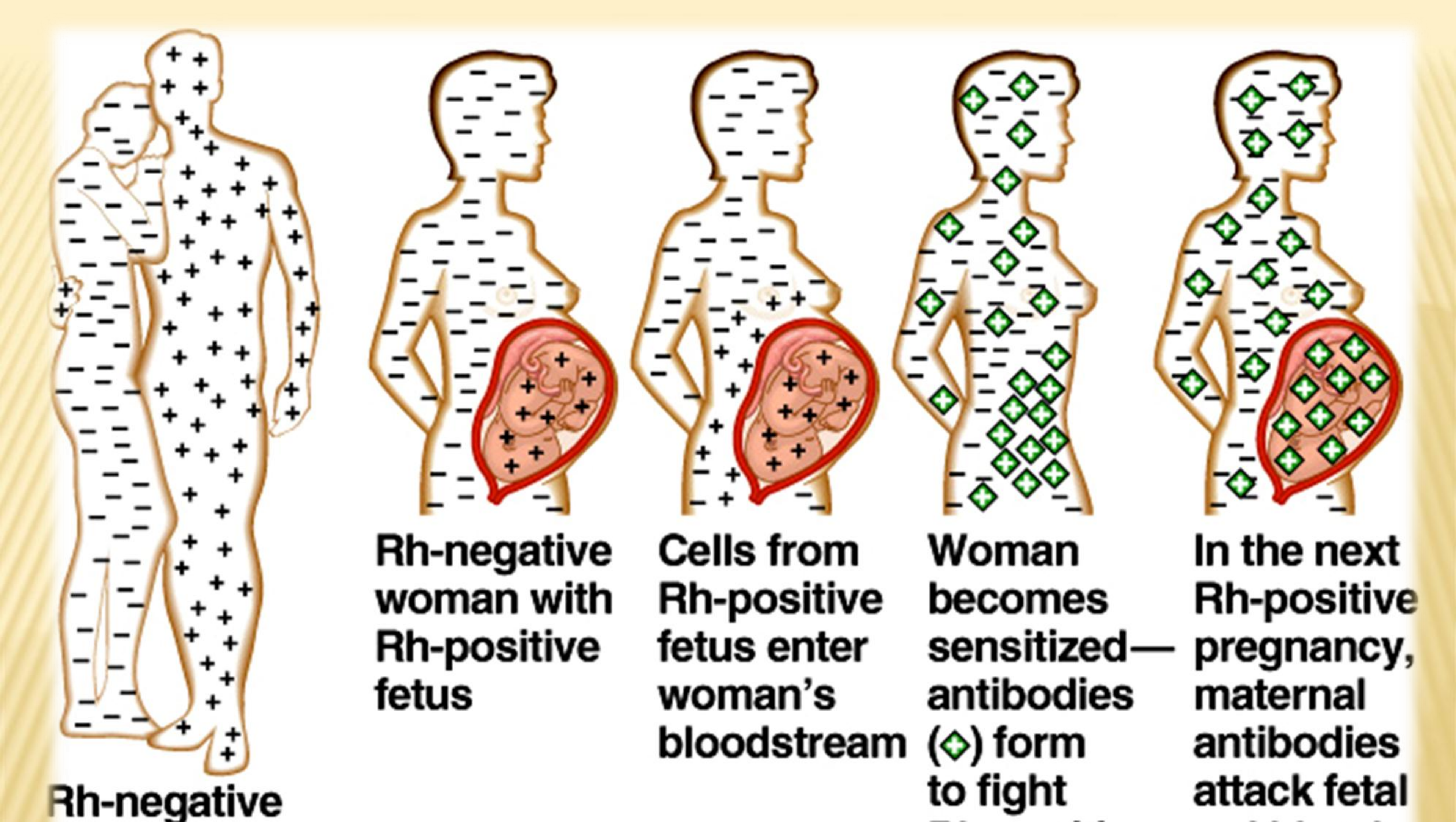


WHAT TYPE OF BLOOD TO GIVE FETUS:

- STORCH negative
- Irradiated
- Fresh Whole Blood (to avoid ↑Ca^{++})
- Maternal blood if possible
- Leukoreduced

RH HDN

- Mother is d negative (d/d) and child is D positive (D/d).
- Most severe form of HDN.
- 33% of HDN is caused by Rh incompatibility.
- Sensitization usually occurs very late in pregnancy, so the first Rh-positive child is not affected.
- Bleeds most often occur at delivery.
- Mother is sensitized.
- Subsequent offspring that are D-positive will be affected



About 1 in 10 pregnancies involve an Rh-negative mother and an Rh-positive father

During delivery, Rh antigens enter mother's circulation through breaks in the placenta

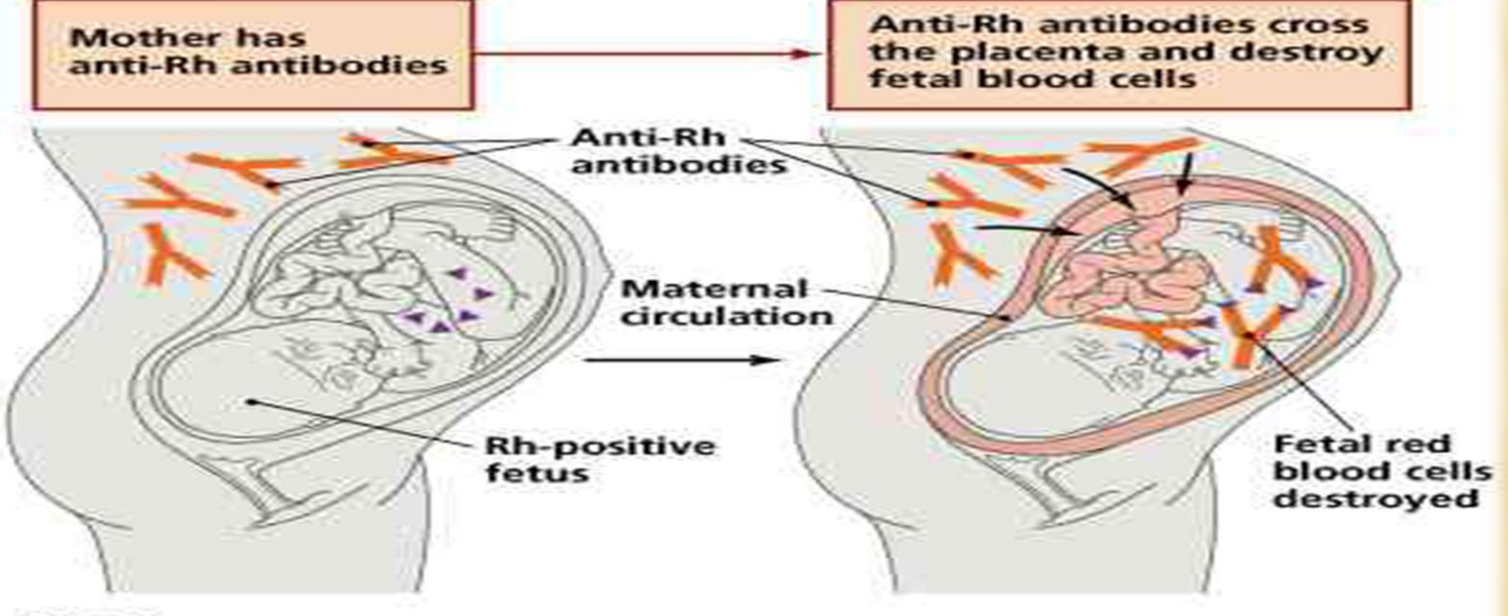
Mother makes anti-Rh antibodies

Rh-negative mother

Anti-Rh antibodies

Rh-positive fetus

(a) First pregnancy



(b) Subsequent pregnancy

FETOMATERNAL HEMORRHAGE

- Sensitization occurs as a result of seepage of fetal cells into maternal circulation as a result of a fetomaternal hemorrhage
  - Placental membrane rupture (7%)
  - Trauma to abdomen
  - Delivery (>50%)
  - Amniocentesis
  - Abortion

FETAL CIRCULATION



Positive cells

MATERNAL CIRCULATION



Invading fetal (positive) cells

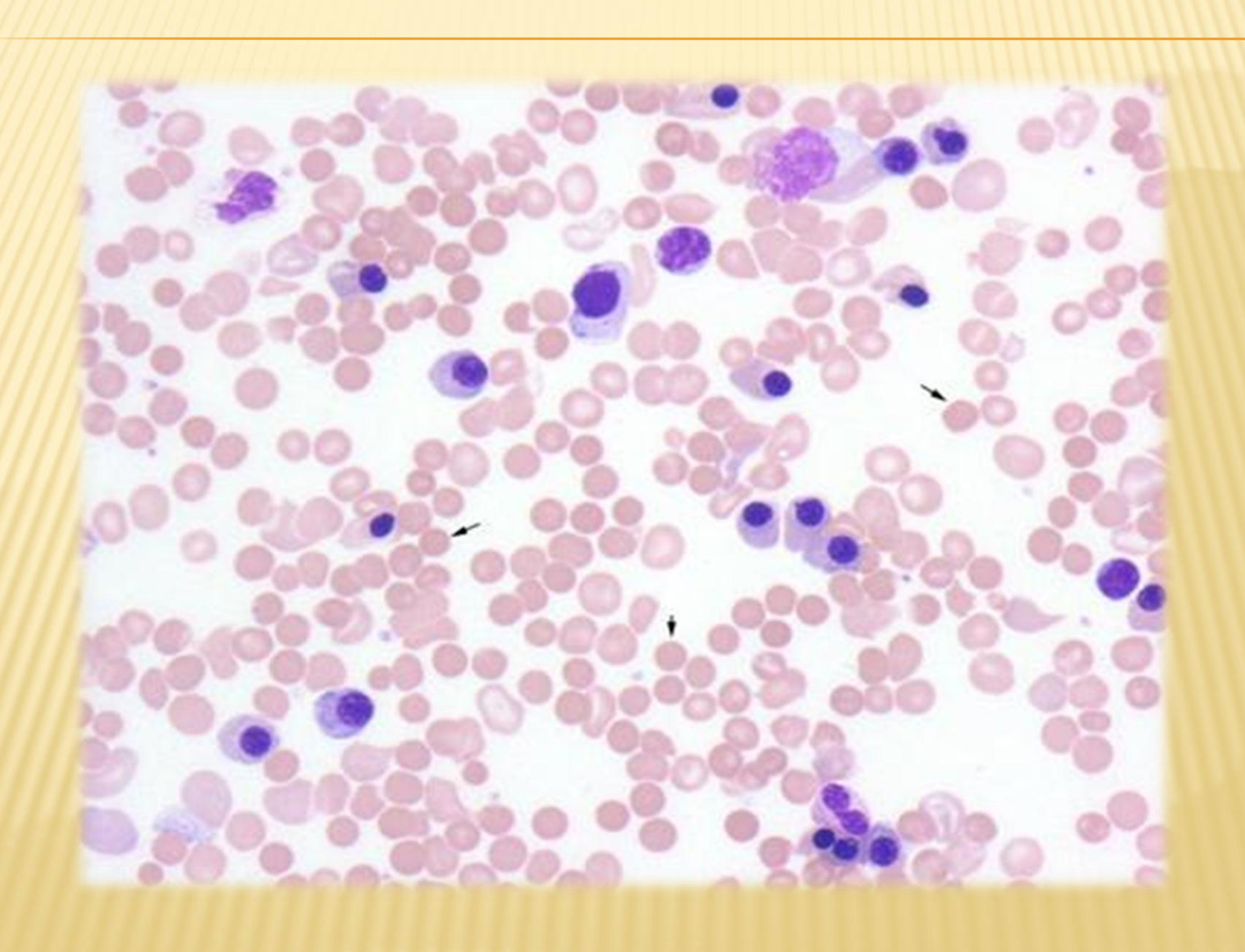
RISK

- Rh-negative women can be exposed to Rh-Positive cells through **transfusion** or **pregnancy**
- Each individual varies in their immune response (depends on amount exposed to)
  - 85% transfused with 200 mL Rh-positive cells will develop anti-D
  - There is only about a 9% chance that Rh-neg mothers pregnant with an Rh-positive child will be stimulated to produce anti-D (without RhIg)

PATHOGENESIS

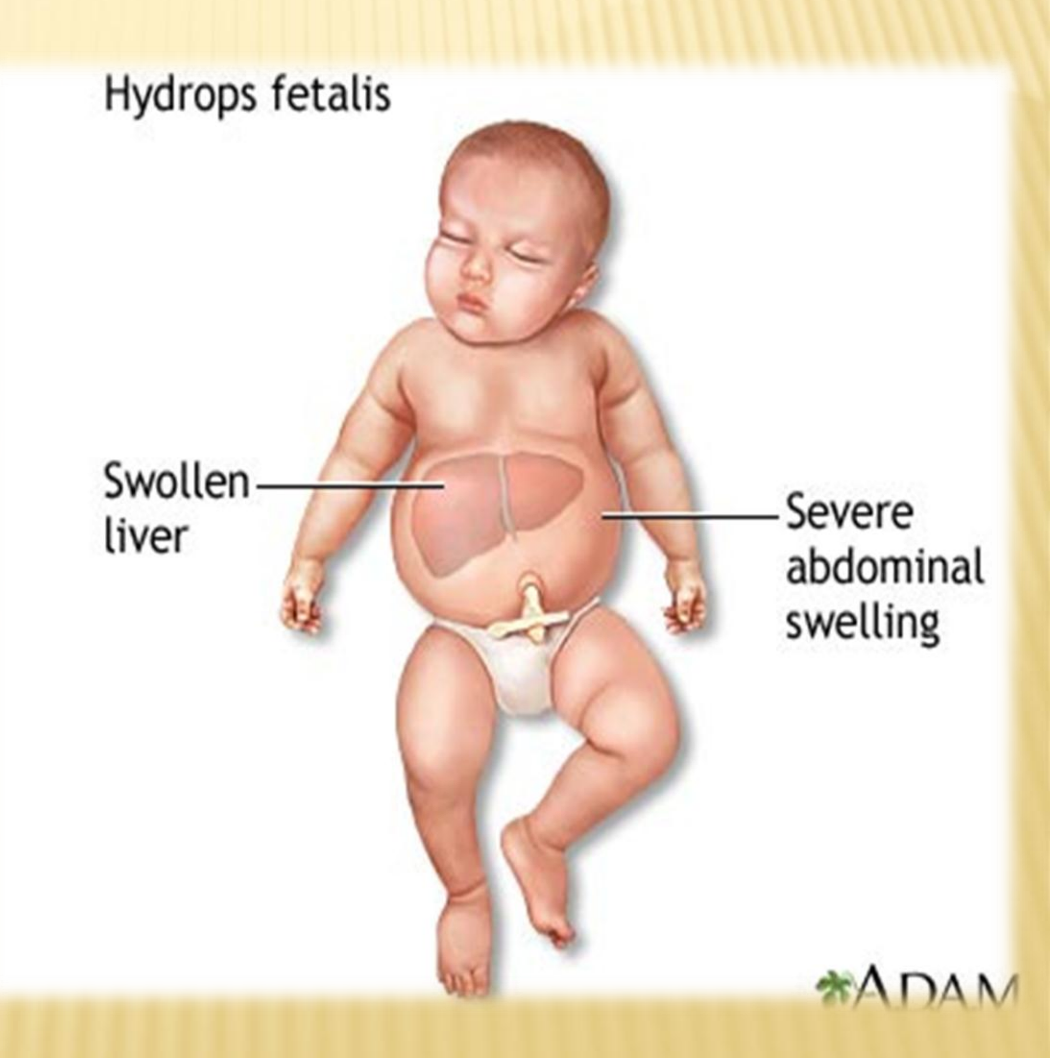
- Maternal IgG attaches to antigens on fetal cells
- Sensitized cells are removed by macrophages in spleen.
- Destruction depends on antibody titer and number of antigen sites.
- IgG has half-life of 25 days, so the condition can range from days to weeks.
- RBC destruction and anemia cause bone marrow to release erythroblasts, hence the name “erythroblastosis fetalis”)

INCREASED IMMATURE RBCS



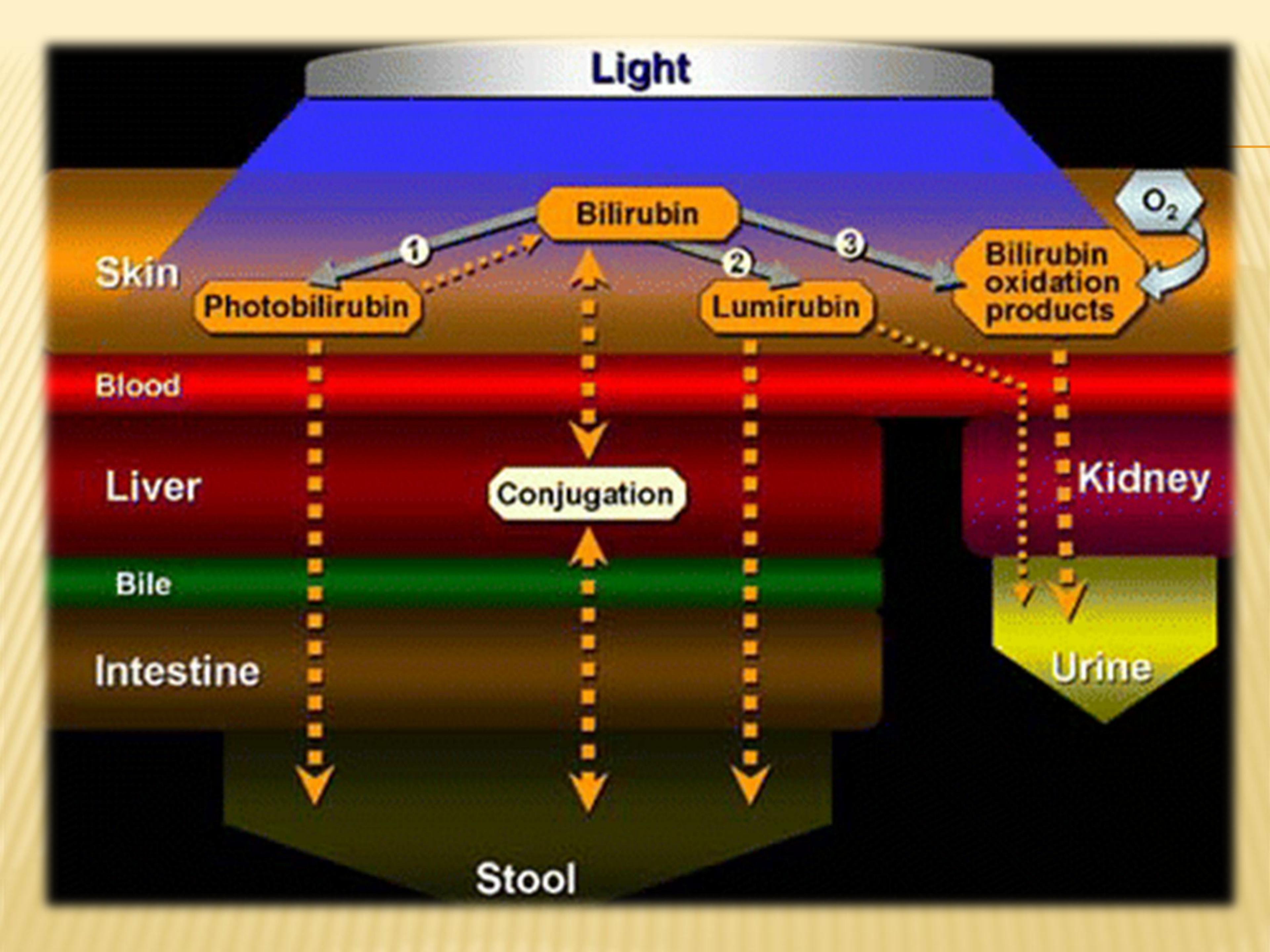
PATHOGENESIS

- When erythroblasts are used up in the bone marrow, **erythropoiesis** in the spleen and liver are increased
  - **Hepatosplenomegaly** (enlarged liver & spleen)
  - **Hypoproteinemia** (from decreased liver function) leads to cardiac failure edema, etc called "Hydrops fetalis"



BILIRUBIN

- Hemoglobin is metabolized to bilirubin
  - Before birth, "**indirect**" bilirubin is transported across placenta and conjugated in maternal liver. "**direct**" where it is excreted
  - After birth, the newborn liver is unable to conjugate the bilirubin
    - Unconjugated ("indirect") bilirubin can reach toxic levels (18-20 mg/dL)
    - This is called **kernicterus** and can lead to permanent brain damage

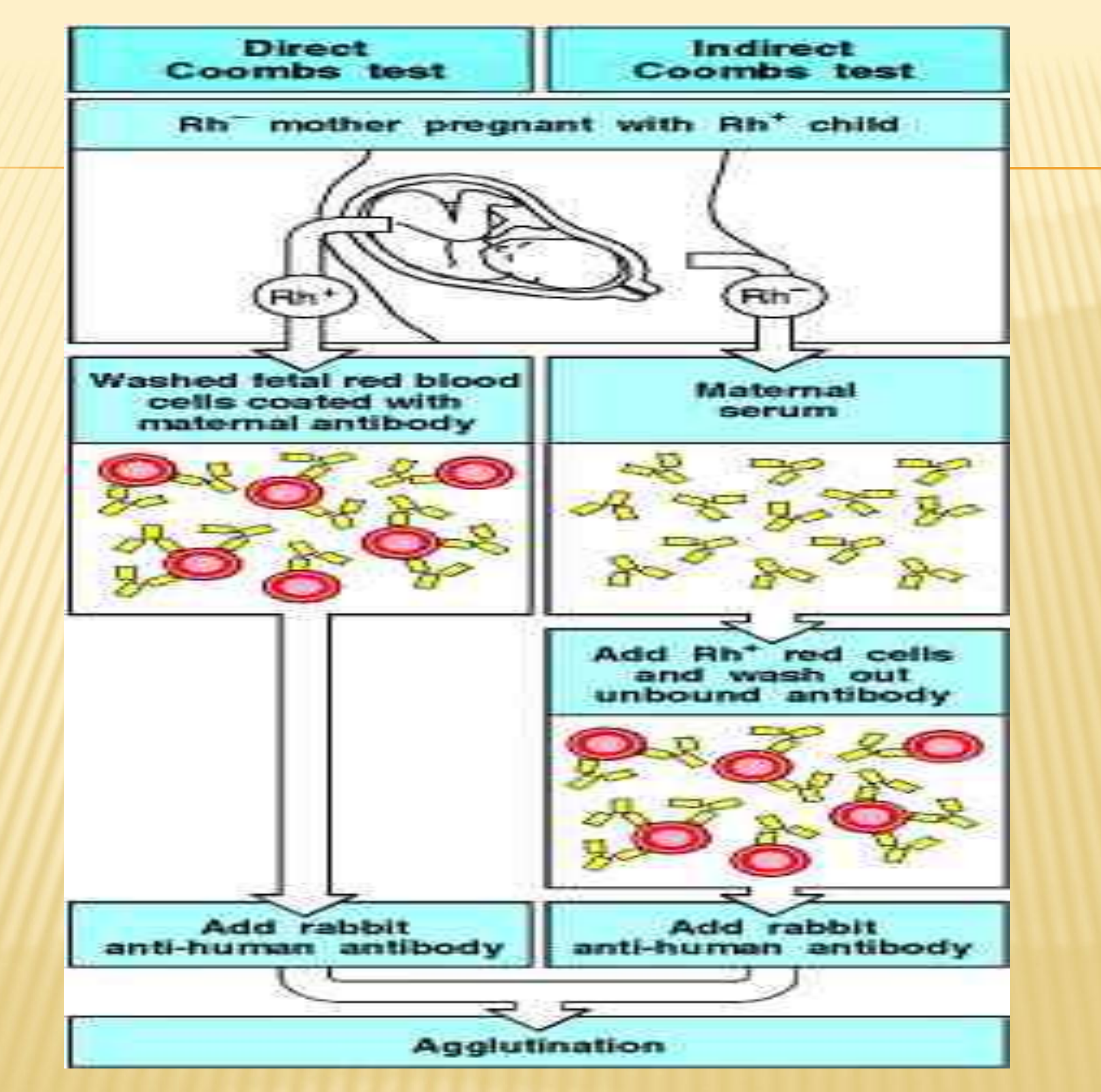

Light
Bilirubin
1
2
3
O_2
Skin
Photobilirubin
Lumirubin
Bilirubin oxidation products
Blood
Liver
Conjugation
Kidney
Bile
Intestine
Urine
Stool

DIAGNOSIS & MANAGEMENT

- Serologic Testing (mother & newborn)
- Amniocentesis and Cordocentesis
- Intrauterine Transfusion
- Early Delivery
- Phototherapy & Newborn Transfusions

SEROLOGIC TESTING ON MOTHER

- ABO and Rh testing
  - Test for D antigen (test for weak D if initially negative)
- Antibody Screen
  - To test detect for IgG alloantibodies that react at 37°C
  - If negative, repeat before RhIg therapy and/or if patient is transfused or has history of antibodies (3rd trimester)
- Antibody ID
  - Weakly reacting anti-D may be due to FMH or passively administered anti-G (RhIg)
  - If antibody is IgG, anti-D is most common followed by anti-K and other Rh antibodies



Direct Coombs test
Indirect Coombs test
Rh⁻ mother pregnant with Rh⁺ child
Rh⁺
Rh⁻
Washed fetal red blood cells coated with maternal antibody
Maternal serum
Add Rh⁺ red cells and wash out unbound antibody
Add rabbit anti-human antibody
Add rabbit anti-human antibody
Agglutination

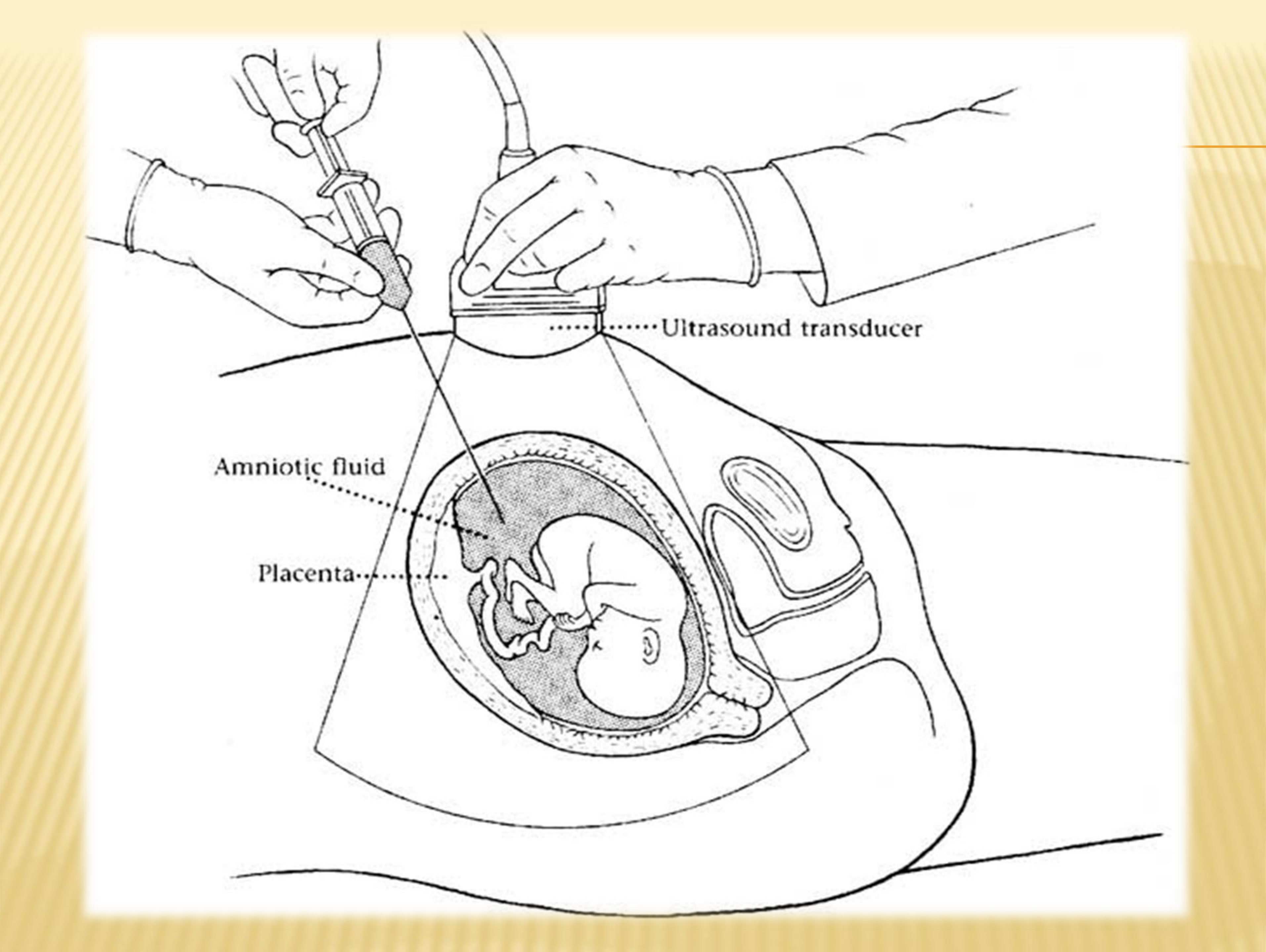
SEROLOGIC TESTING (CONT'D)

Antibody titration

- Antibody concentration is determined by antibody titration.
- Mother's serum is diluted to determine the highest dilution that reacts with reagent RBCs at 37°C (60 min).
- First sample is frozen and run with later specimens.
- Testing is repeated at 16 and 22 weeks and 1- to 4- week.
  - A titer of 16-32 is significant
  - >16 should be repeated at 18-20 weeks' gestation
  - >32 indicates a need for amniocentesis or cordocentesis between 18-24 weeks' gestation
  - <32 is repeated every 4 weeks (18-20 weeks) and every 2-4 weeks (third trimester).

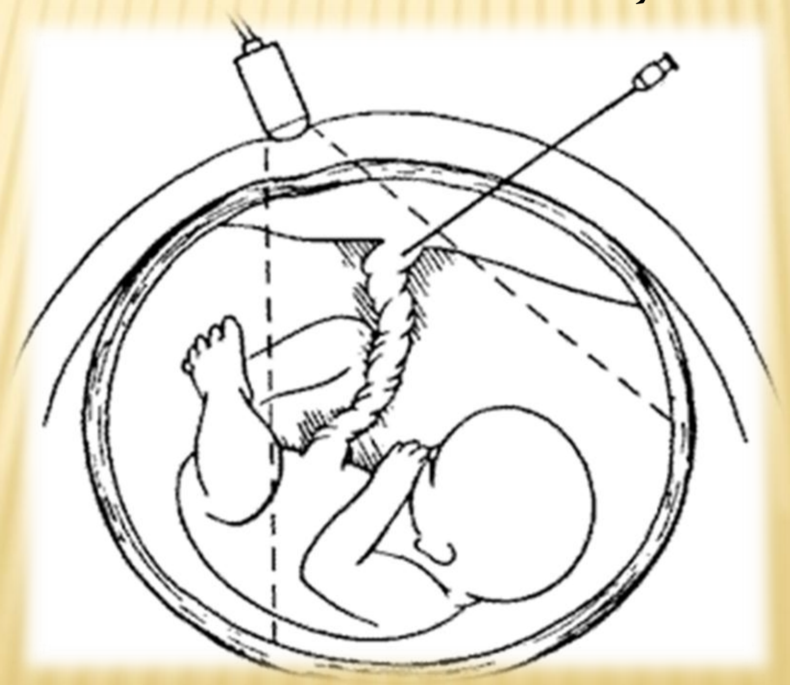
AMNIOCENTESIS & CORDOCENTESIS

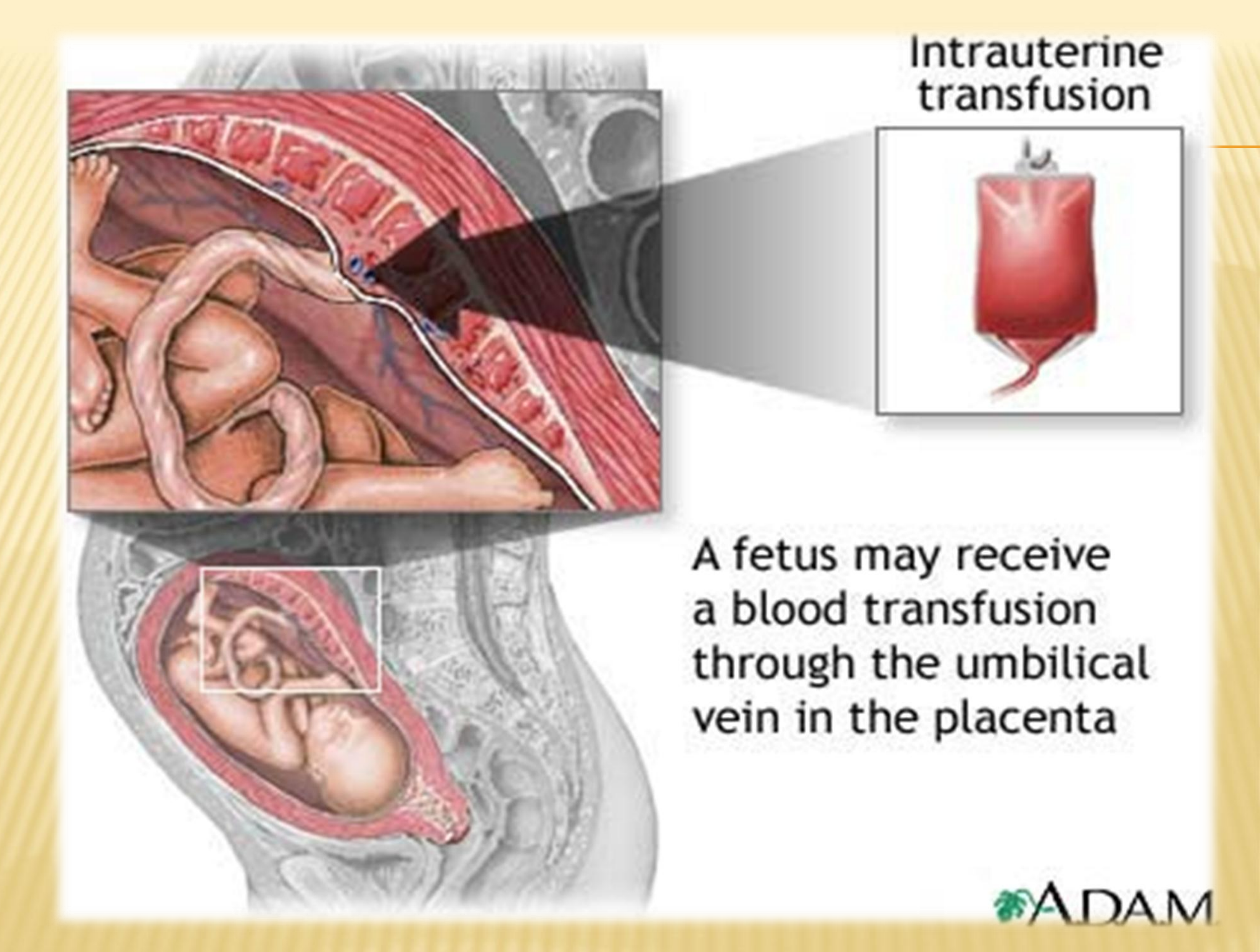
- About 18-20 weeks' gestation
- Cordocentesis takes a sample of umbilical vessel to obtain blood sample
- Amniocentesis assesses the status of the fetus using amniotic fluid
  - Fluid is read on a spectrophotometer (350-700 nm)
  - Change in optical density (ΔOD) above the baseline of 450 nm is the bilirubin measurement


Ultrasound transducer
Amniotic fluid
Placenta

WHAT TO DO?

- Intrauterine transfusion is done :
  - Removes bilirubin
  - Removes sensitized RBCs
  - Removes antibody




Intrauterine
transfusion
A fetus may receive
a blood transfusion
through the umbilical
vein in the placenta
A.D.A.M.

OTHER TREATMENTS

- **Early Delivery**
  - If labor is induced, fetal lung maturity must be determined using the lecithin/sphingomyelon (L/S) ratio (thin layer chromatography) to avoid respiratory distress syndrome
- **Phototherapy (after birth)**
  - Change unconjugated bilirubin to biliverdin
  - May avoid the need for exchange transfusion
- **Newborn transfusion**
  - Small aliquots of blood (PediPak)
  - Corrects anemia

PREVENTION

- RhIg (RhoGAM®) is given to the mother to prevent immunization to the D antigen
  - "Fools" mom into thinking she has the antibody
  - RhIg (1 dose) is given at 28 weeks' gestation
  - RhIg attaches to fetal RBCs in maternal circulation and are removed in maternal spleen; this prevents alloimmunization by mother

POSTPARTUM ADMINISTRATION OF RHIG

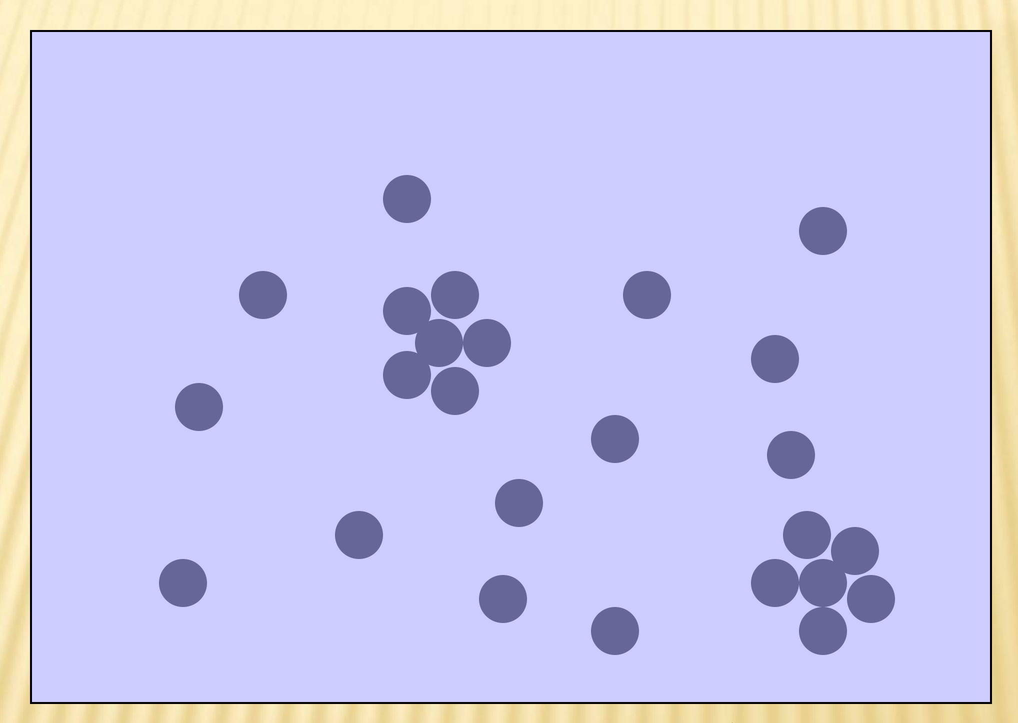
- Another dose of RhIg should be given to the mother within 72 hours of delivery (even if stillborn)
  - Mother should be D negative
  - Newborn should be D positive or weak D
  - About 10% of the original dose will be present at birth, so it's important to give another dose to prevent immunization

DOSE

- Each vial of RhIg contains enough anti-D for protect
  - One vial contains 300 μg of anti-D
  - Given intramuscularly of intravenously
  - Massive fetomaternal hemorrhage (>30 mL) requires more than one vial

ROSETTE TEST

- A qualitative measure of fetomaternal hemorrhage



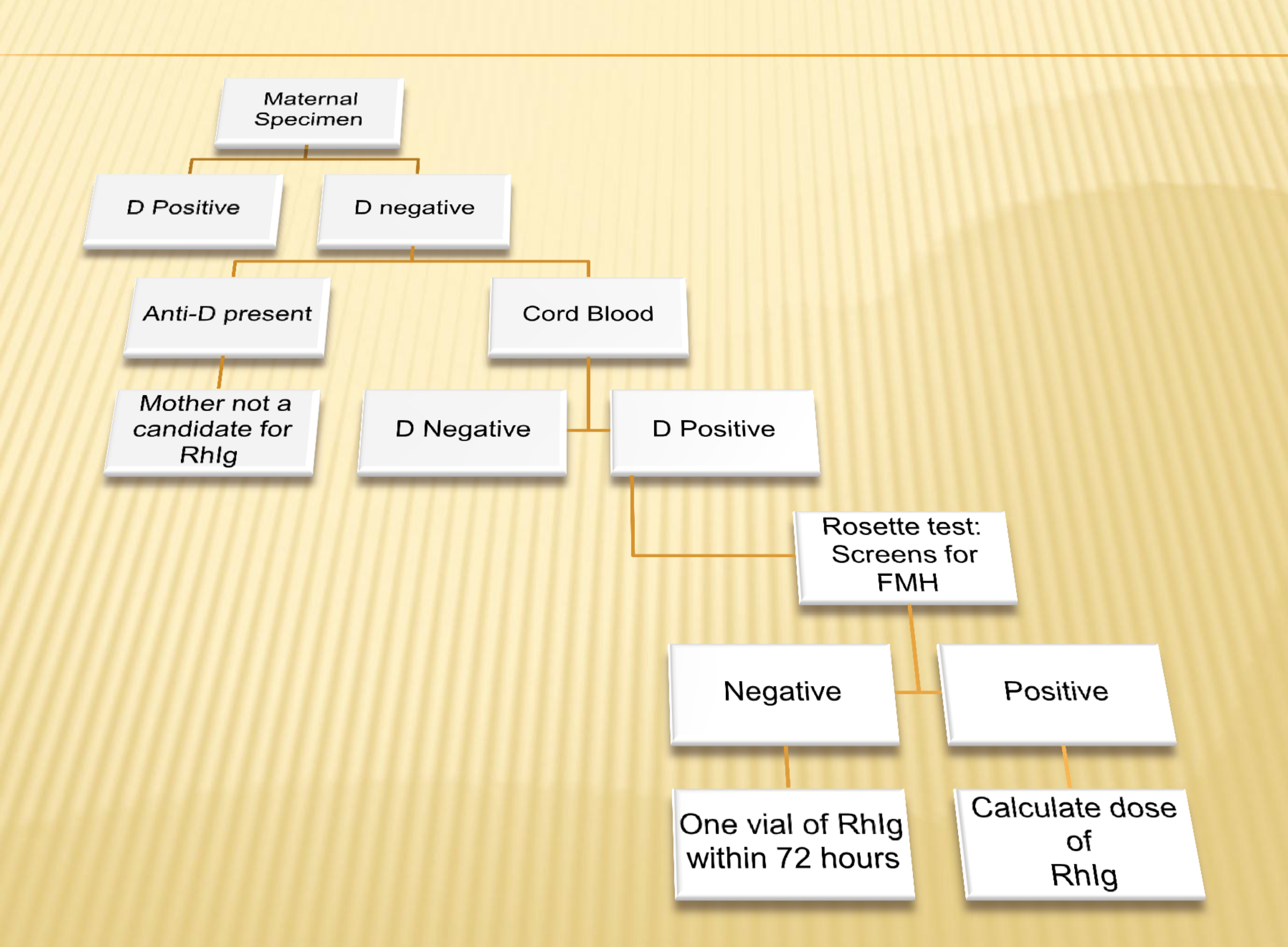
Fetomaternal Hemorrhage:

<1 rosette per 3 lpf = 1 dose of RhIg

>1 rosette per 3 lpf = Quantitate bleed

CONSIDERATIONS

- RhIg is of no benefit once a person has formed anti-D
- It is VERY important to distinguish the presence of anti-D as:
  - Residual RhIg from a previous dose OR
  - True immunization from exposure to D+ RBCs
- RhIg is not given to the mother if the infant is D negative (and not given to the infant)


Maternal Specimen
D Positive
D negative
Anti-D present
Cord Blood
Mother not a candidate for RhIg
D Negative
D Positive
Rosette test: Screens for FMH
Negative
Positive
One vial of RhIg within 72 hours
Calculate dose of RhIg